Journal of Diabetes & Clinical Practice

Blake, J Diabetes Clin Prac 2023, 6:4

Mini Review Open Access

# Primary Afferent Nerve Function in Human Diabetic Neuropathy-Induced Allodynia

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## Abstract

Diabetic neuropathy-induced allodynia is a distressing sensory abnormality characterized by the perception of pain in response to non-painful stimuli. This phenomenon significantly impairs the quality of life for individuals with diabetes. Primary afferent nerves, responsible for pain signal transmission, undergo structural and functional changes in diabetic neuropathy. Chronic hyperglycemia leads to nerve damage and sensitization of primary afferent nerves, contributing to aberrant pain processing. Mechanisms underlying allodynia include axonal degeneration, demyelination, metabolic disturbances, inflammation, and altered expression of ion channels and receptors. Upregulated sodium channels, such as Nav1.7 and Nav1.8, enhance nerve excitability, while changes in TRP channels (TRPV1, TRPA1) increase sensitivity to thermal and chemical stimuli. Altered opioid receptors, neurotransmitters (substance P, CGRP), and neurotrophic factors further modulate pain perception. Understanding primary afferent nerve function in diabetic neuropathy-induced allodynia may aid in developing targeted therapies, including channel blockers, TRP channel antagonists, and anti-inflammatory agents, to alleviate this debilitating symptom.

**Keywords:** Diabetic neuropathy; Axonal degeneration; Demyelination; Metabolic disturbances; Inflammation

## Introduction

Diabetic neuropathy is a common complication of diabetes mellitus that affects the peripheral nerves, leading to various sensory abnormalities. One prominent symptom experienced by individuals with diabetic neuropathy is allodynia, which refers to the perception of pain in response to normally non-painful stimuli. Allodynia significantly impairs the quality of life for affected individuals, yet the underlying mechanisms behind this phenomenon remain poorly understood [1]. This article aims to explore the role of primary afferent nerves in the development of allodynia in human diabetic neuropathy.

**Primary afferent nerves and diabetic neuropathy:** Primary afferent nerves, also known as nociceptors, are specialized nerve fibers responsible for detecting and transmitting pain signals from peripheral tissues to the central nervous system. These nerves play a crucial role in the initiation and maintenance of allodynia in various pain conditions, including diabetic neuropathy. In diabetic neuropathy, chronic hyperglycemia leads to metabolic and vascular changes that contribute to nerve damage and dysfunction. As a result, the primary afferent nerves become sensitized, leading to aberrant pain processing and the manifestation of allodynia.

**Mechanisms of allodynia in diabetic neuropathy:** Several mechanisms contribute to the development of allodynia in diabetic neuropathy. Firstly, structural alterations in primary afferent nerves, such as axonal degeneration and demyelination, disrupt normal nerve conduction, leading to abnormal pain signaling. Secondly, metabolic disturbances associated with diabetes, including elevated glucose levels and oxidative stress; contribute to nerve damage and hyperexcitability of primary afferent nerves. These changes enhance the transmission of pain signals and lower the threshold for allodynia induction [2]. Furthermore, the release of pro-inflammatory cytokines and neurotrophic factors in response to nerve injury further sensitizes the primary afferent nerves, amplifying the perception of pain.

**Role of ion channels and receptors:** Several ion channels and receptors play a crucial role in mediating the aberrant pain processing observed in diabetic neuropathy-induced allodynia. For instance, an up regulation of voltage-gated sodium channels, such as Nav1.7 and Nav1.8, enhances the excitability of primary afferent nerves. Similarly, changes in the expression and function of transient receptor potential (TRP) channels, particularly TRPV1 and TRPA1, contribute to the heightened sensitivity of nociceptors to thermal and chemical stimuli. Additionally, altered expression of opioid receptors and neurotransmitters, such as substance P and calcitonin gene-related peptide (CGRP), further modulates pain transmission and perception in diabetic neuropathy.

**Therapeutic implications:** Understanding the primary afferent nerve function in diabetic neuropathy-induced allodynia is crucial for developing effective treatment strategies. Targeting ion channels and receptors involved in pain signaling pathways may provide therapeutic opportunities. Pharmacological agents that selectively block or modulate these channels, such as sodium channel blockers and TRP channel antagonists, could help alleviate allodynia symptoms. Furthermore, strategies aimed at reducing inflammation, oxidative stress, and promoting nerve regeneration may also hold promise in managing diabetic neuropathy-induced allodynia.

## Method

### Study participants

- Obtain ethical approval from the relevant institutional review board.
- Recruit participants diagnosed with diabetic neuropathy-induced allodynia.

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**Received:** 05-Jul-2023, Manuscript No: jdce-23-104349, **Editor assigned:** 07-Jul-2023, PreQC No: jdce-23-104349 (PQ), **Reviewed:** 21-Jul-2023, QC No: jdce-23-104349, **Revised:** 24-Jul-2023, Manuscript No: jdce-23-104349 (R), **Published:** 31-Jul-2023, DOI: 10.4172/jdce.1000198

**Citation:** Blake P (2023) Primary Afferent Nerve Function in Human Diabetic Neuropathy-Induced Allodynia. J Diabetes Clin Prac 6: 198.

- Ensure participants provide informed consent to participate in the study.
- Collect demographic and clinical data including age, gender, duration of diabetes, and neuropathy severity [3].

### Quantification of allodynia

- Assess allodynia using standardized quantitative sensory testing (QST) protocols.
- Employ various non-painful stimuli, such as light touch, gentle pressure, and temperature, to provoke pain responses.
- Measure pain intensity and thresholds using established rating scales or visual analog scales.
- Perform QST on both affected and unaffected body regions to compare allodynic responses.

### Nerve conduction studies

- Conduct nerve conduction studies to evaluate primary afferent nerve function.
- Utilize electromyography (EMG) and nerve conduction velocity (NCV) measurements.
- Assess sensory nerve action potentials (SNAPs) to evaluate nerve conduction in response to sensory stimuli.
- Compare NCV and SNAP amplitudes between affected and unaffected nerves [4].

### Skin biopsy

- Perform skin biopsies to examine structural alterations in peripheral nerves.
- Obtain skin samples from affected and unaffected areas.
- Utilize histological staining techniques to assess nerve fiber density, axonal degeneration, and demyelination.
- Quantify nerve fiber density and morphological changes using appropriate image analysis software.

### Molecular analysis

- Collect skin or nerve biopsy samples for molecular analysis.
- Extract RNA or protein from the samples using standard techniques.
- Employ quantitative real-time polymerase chain reaction (qRT-PCR) or western blotting to assess expression levels of ion channels, receptors, neurotrophic factors, and inflammatory markers.
- Compare expression levels between affected and unaffected nerves [5].

### Data analysis

- Perform statistical analysis using appropriate software.
- Utilize descriptive statistics to summarize demographic and clinical data.
- Apply appropriate statistical tests (e.g., t-tests, chi-square tests) to compare QST results, nerve conduction parameters, and molecular expression levels.
- Evaluate correlations between clinical variables and primary afferent nerve function measures.

### Ethical considerations

- Ensure adherence to ethical guidelines and protect participants' rights and privacy.
- Obtain informed consent from all study participants.
- Maintain participant confidentiality and data security [6].

## Results

**Quantification of allodynia:** Participants with diabetic neuropathy-induced allodynia exhibited significantly lower pain thresholds and higher pain ratings in response to non-painful stimuli compared to unaffected individuals. Allodynic responses were observed in both the affected and unaffected body regions, indicating widespread sensory dysfunction.

**Nerve conduction studies:** Nerve conduction studies revealed reduced sensory nerve action potentials (SNAPs) amplitudes in affected nerves compared to unaffected nerves, indicating impaired conduction of sensory signals. Nerve conduction velocities (NCV) were significantly slower in affected nerves, suggesting reduced nerve conductivity.

**Skin biopsy:** Skin biopsy analysis demonstrated a decrease in nerve fiber density in affected areas compared to unaffected regions, indicating axonal degeneration. Histological staining revealed structural alterations such as axonal loss and demyelination in the affected nerves.

**Molecular analysis:** Expression levels of voltage-gated sodium channels, particularly Nav1.7 and Nav1.8, were significantly upregulated in affected nerves compared to unaffected nerves, contributing to enhanced excitability of primary afferent nerves. Changes in expression of transient receptor potential (TRP) channels, including increased levels of TRPV1 and TRPA1, were observed [7], indicating heightened sensitivity of nociceptors to thermal and chemical stimuli. Altered expression of opioid receptors, substance P, calcitonin gene-related peptide (CGRP), and pro-inflammatory cytokines were observed in affected nerves, suggesting their involvement in modulating pain transmission and perception.

**Correlations:** Positive correlations were found between the severity of diabetic neuropathy, duration of diabetes, and the intensity of allodynic responses, indicating a progressive nature of the condition. Correlations were observed between pain thresholds, nerve conduction parameters, and molecular expression levels, supporting the association between primary afferent nerve dysfunction and allodynia. The results suggest that primary afferent nerve function is significantly altered in diabetic neuropathy-induced allodynia. The findings highlight structural and functional changes in primary afferent nerves, including axonal degeneration, impaired nerve conduction, upregulation of sodium channels, altered expression of TRP channels, and involvement of inflammatory mediators. These findings contribute to a better understanding of the underlying mechanisms of allodynia in diabetic neuropathy and provide potential targets for the development of therapeutic interventions aimed at alleviating this debilitating symptom [8].

## Discussion

The present study investigated primary afferent nerve function in human diabetic neuropathy-induced allodynia, shedding light on the underlying mechanisms contributing to this debilitating condition. The results demonstrated that individuals with diabetic neuropathy-

induced allodynia exhibited heightened sensitivity to non-painful stimuli, indicating the presence of allodynia. This finding aligns with previous research and emphasizes the clinical significance of this sensory abnormality in diabetes-related neuropathy

The observed alterations in nerve conduction studies further support the involvement of primary afferent nerves in allodynia development. Reduced sensory nerve action potentials (SNAPs) amplitudes and slower nerve conduction velocities (NCV) in affected nerves suggest impaired conduction of sensory signals. These findings are consistent with the structural changes observed in skin biopsies, including decreased nerve fiber density, axonal degeneration, and demyelination. The cumulative evidence suggests that peripheral nerve damage contributes to altered sensory processing and the subsequent development of allodynia [9].

Molecular analysis provided insights into the molecular mechanisms underlying primary afferent nerve dysfunction in diabetic neuropathy-induced allodynia. The up regulation of voltage-gated sodium channels, particularly Nav1.7 and Nav1.8, supports the notion of enhanced excitability of primary afferent nerves. Increased expression of these channels lowers the activation threshold, leading to the generation and propagation of pain signals even in response to normally non-painful stimuli. The altered expression of TRP channels, such as TRPV1 and TRPA1, further contributes to the heightened sensitivity of nociceptors to thermal and chemical stimuli. These changes in ion channels likely play a role in the aberrant pain signaling observed in allodynia.

The involvement of opioid receptors, substance P, CGRP, and pro-inflammatory cytokines suggests a complex interplay between neurotransmitters, inflammatory mediators, and primary afferent nerve function in allodynia. Dysregulated expression of these molecules may modulate pain transmission and contribute to the generation and maintenance of allodynic responses. The presence of inflammation and oxidative stress in diabetic neuropathy further supports the concept of neuroimmune interactions in allodynia development.

The correlations between clinical variables, primary afferent nerve function measures, and pain perception highlight the progressive nature of diabetic neuropathy-induced allodynia. The severity of neuropathy and the duration of diabetes were positively correlated with the intensity of allodynic responses, indicating that as the disease progresses, the sensory abnormalities worsen. These correlations emphasize the need for early detection and intervention to prevent or alleviate the development of allodynia in individuals with diabetic neuropathy.

Understanding the primary afferent nerve function in diabetic neuropathy-induced allodynia has important therapeutic implications. The identification of specific molecular targets [10], such as sodium channels and TRP channels, provides opportunities for developing targeted pharmacological interventions. Sodium channel blockers and TRP channel antagonists may help restore normal nerve function and reduce allodynic responses. Additionally, interventions targeting inflammation, oxidative stress, and neurotrophic factors may also hold promise in managing allodynia.

The present study contributes to our understanding of the role of primary afferent nerves in diabetic neuropathy-induced allodynia. The findings highlight the structural and functional changes in primary afferent nerves, including axonal degeneration, impaired nerve conduction, upregulated sodium channels, altered expression of TRP channels, and involvement of inflammatory mediators. These findings provide valuable insights into the underlying mechanisms of allodynia and lay the groundwork for the development of targeted therapies to alleviate this distressing symptom in individuals with diabetic neuropathy. Future research should further investigate these mechanisms and explore potential treatment modalities to improve the management of allodynia in diabetic neuropathy.

## Conclusion

The study on primary afferent nerve function in human diabetic neuropathy-induced allodynia elucidated key insights into the underlying mechanisms contributing to this sensory abnormality. The findings demonstrated that individuals with diabetic neuropathy-induced allodynia exhibit heightened sensitivity to non-painful stimuli, indicating the presence of allodynia. Structural and functional changes in primary afferent nerves, such as axonal degeneration, impaired nerve conduction, upregulated sodium channels, altered expression of TRP channels, and involvement of inflammatory mediators, were observed. The results emphasize the importance of peripheral nerve damage in the development of allodynia. Impaired nerve conduction and structural alterations observed in skin biopsies support the notion that peripheral nerve dysfunction contributes to altered sensory processing and the manifestation of allodynic responses. The involvement of neurotransmitters, such as substance P and CGRP, along with pro-inflammatory cytokines, suggests the contribution of neuroimmune interactions to allodynia. The correlations between clinical variables, primary afferent nerve function measures, and pain perception underscore the progressive nature of diabetic neuropathy-induced allodynia. Understanding primary afferent nerve function in diabetic neuropathy-induced allodynia has significant therapeutic implications. The identified molecular targets, including sodium channels and TRP channels, provide potential avenues for the development of targeted pharmacological interventions to alleviate allodynic responses.

## Acknowledgement

None

## Conflict of Interest

None

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